Effect of multivitamin and multimineral supplements on morbidity from infections in older people (MAVIS trial): pragmatic, randomised, double blind, placebo controlled trial

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Abstract

Objective To examine whether supplementation with multivitamins and multiminerals influences self reported days of infection, use of health services, and quality of life in people aged 65 or over.
Design Randomised, placebo controlled trial, with blinding of participants, outcome assessors, and investigators.
Setting Communities associated with six general practices in Grampian, Scotland.
Participants 910 men and women aged 65 or over who did not take vitamins or minerals.
Interventions Daily multivitamin and multimineral supplementation or placebo for one year.
Main outcome measures Primary outcomes were contacts with primary care for infections, self reported days of infection, and quality of life. Secondary outcomes included antibiotic prescriptions, hospital admissions, adverse events, and compliance.
Results Supplementation did not significantly affect contacts with primary care and days of infection per person (incidence rate ratio 0.96, 95% confidence interval 0.78 to 1.19 and 1.07, 0.90 to 1.27). Quality of life was not affected by supplementation. No statistically significant findings were found for secondary outcomes or subgroups.
Conclusion Routine multivitamin and multimineral supplementation of older people living at home does not affect self reported infection related morbidity.
Trial registration ISRCTN: 66376460.

Introduction

Respiratory tract and urinary tract infections are common reasons for older people to visit their doctor,[1] and viral respiratory tract infections may precipitate hospital admission in people with diabetes or cardiac or chronic obstructive pulmonary diseases.[2] Ageing is associated with dysregulation of the immune system.[3] Declining immunity can lead to infection and depletion of nutritional reserves, which may already be suboptimal for host defences.[4]

The UK national diet and nutrition survey of older people found evidence of multiple nutritional deficiencies.[5] The prevalence of deficiencies on blood testing ranged from about 10% for iron, vitamin C, red cell folate, thiamine, and vitamin D in people living in the community to about 40% for vitamin C, riboflavin, and vitamin D in those living in care. Deficiencies were greater in Scotland than in southern England and greater in those aged 75 or over.

At least 25% of older people in the United Kingdom take nutritional supplements.[5] Multivitamin and multimineral supplements are widely available and most brands have similar contents. Whether such supplementation influences infections in older people, particularly those not in nursing homes, is unclear from randomised controlled trials. A recent systematic review concluded that evidence for the routine use of multivitamin and multimineral supplements in older people was weak and conflicting and that further randomised controlled trials were recommended.[6] That review included trials by Chandra,[7 8] whose work has been questioned, leading one editor to retract a publication from one of the trials.[7 9] An update to the review has been published.[10]

Supplementation is a low cost option for improving nutritional status. We undertook a pragmatic, randomised, placebo controlled trial to examine whether supplementation influences self reported infections, use of health services, and quality of life in people aged 65 or over.

Participants and methods

Participants were recruited from six general practices in Grampian, Scotland between February and December 2002. All people aged 65 or over who were registered with the practices were eligible, irrespective of chronic illness, unless their doctors considered them too unwell. Exclusion criteria were use of vitamin, mineral, or fish oil supplements in the previous three months (one month in the case of water soluble vitamins) or vitamin B_{12} injection in the past three months. Written informed consent was collected.

Participants were recruited in their practice or at home by an experienced nurse or dietician. Detailed instructions were given about trial drugs, completion of daily diaries on infection and any contacts with primary care for infections, which were returned monthly, and the need to avoid vitamin or mineral supplements from other sources during the trial.

Interventions

Participants were randomised to one tablet daily of a multivitamin and multimineral supplement or a matched sorbitol placebo. Supplements were 800 µg vitamin A (acetate), 60 mg vitamin C, 5 µg vitamin D_3, 10 mg vitamin E (D, L-α tocopheryl

acetate), 1.4 mg thiamin (mononitrate), 1.6 mg riboflavin, 18 mg niacin (nicotinamide), 6 mg pantothenic acid (calcium D-pantothenate), 2 mg pyridoxine (hydrochloride), 1 µg vitamin B_{12}, 200 µg folic acid, 14 mg iron (fumurate), 150 µg iodine (potassium iodide), 0.75 mg copper (gluconate), 15 mg zinc (oxide), and 1 mg manganese (sulphate). The supplement provided between 50-210% of UK reference nutrient intakes.[11] Tablets were purchased from a commercial supplier and given to participants for one year.

Outcomes

Predefined primary outcomes were number of contacts with primary care (doctor and other primary care workers, in person or by phone) for infection, number of self reported days of infection, and health related quality of life measured by the EuroQol[12] and SF-12.[13] The EuroQol is a generic questionnaire used to provide a single score for health related quality of life; responses to the EuroQol were converted to a score using the EuroQol UK population tariff.[14] The SF-12 is a generic measure of health related quality of life, including physical functioning, social functioning, role limitations due to physical or emotional problems, mental health, vitality, pain, and perception of general health. We used prespecified procedures to code diaries for contacts with primary care for infection and days of infection.

Predefined secondary outcomes were number of antibiotic prescriptions in primary care, number of days that antibiotics were prescribed, number of hospital admissions (including those related to infection), number of days in hospital with infection, number of infection related and all outpatient visits, adverse events reported by participants, and compliance with trial drugs (from diaries submitted monthly in all participants and tablet count at six and 12 months in a random sample of 10% of participants). Hospital data were obtained from computerised patient administration systems and hospital and general practice records.

General practice records were the only source of information on contacts with primary care and antibiotic prescriptions in over 94% of cases. Missing data were supplemented with participants' diary information when deaths subsequently occurred and the health board had removed the general practice notes, or when participants gave details of antibiotic prescriptions missing from the general practice records.

We carried out prespecified subgroup analyses for ages 65-74, 75-84, and ≥85 (the last two categories being subsequently combined because few participants were aged ≥85), sex, type of accommodation (community, or in care, such as a nursing home), and nutrition risk score (predictive of no deficiency versus one deficiency in any of four groups).

We used a nutrition assessment questionnaire for detecting older people at risk of nutritional deficiencies in vitamin C, vitamin D, folate, or iron.[15] We developed questions from responses to a questionnaire and blood levels of nutritional status in a healthy local population of older people without evidence of infection.[16]

Sample size

We determined that we would need 900 participants to provide 80% power (5% significance, two-tailed) to detect a 25% reduction in contacts with primary care for infection, where 40% of this population in the United Kingdom seek help from primary care for infections in any year.[1] We assumed a dropout rate of 20%. Our trial would be able to identify, with the same power, relatively smaller effects on the other primary outcome of days of infection.

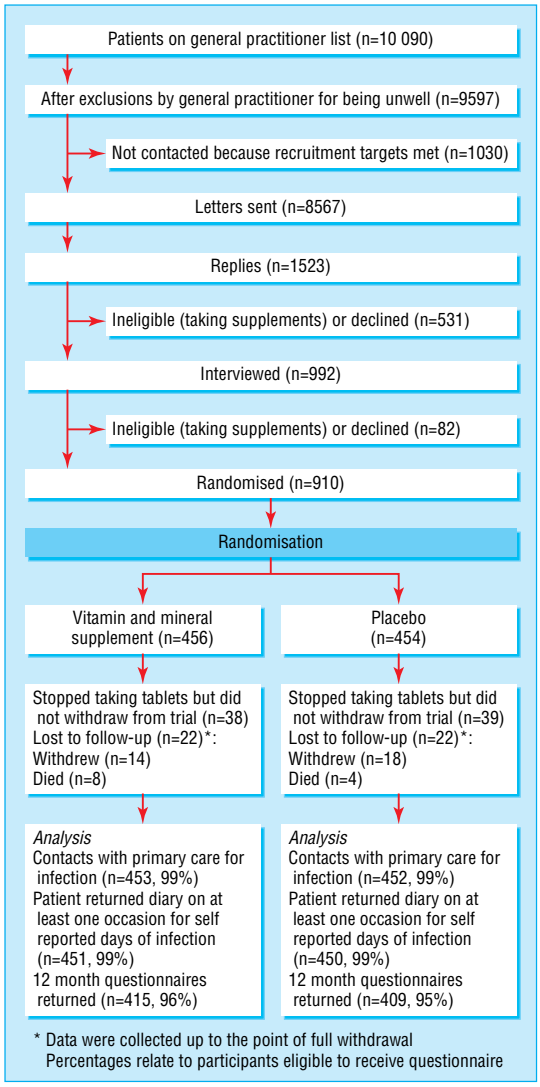

Fig 1 Flow of participants through trial

Randomisation and blinding

At recruitment, participants were randomly allocated to intervention or placebo by batch numbers generated by a password protected computer program. The program could be accessed by only the data programmer, blind to treatment allocation. The identity of the tablets was concealed in a double envelope sent by the manufacturer, which was kept locked in a cabinet during the trial. Randomisation was stratified by general practice and minimised by age (65-74, 75-84, ≥85), sex, and type of accommodation (community or in care).

Assessors blind to trial allocation collected participant reported primary care and hospital data. Statisticians undertook analysis also blind to trial allocation. Blinding of researchers, participants, and health professionals was maintained until completion of the analyses.

Quality assurance

The trial was conducted according to the Medical Research Council's guidelines for good clinical practice in clinical trials.[17] All data collected were subjected to quality assurance procedures. Two researchers independently entered a 10% random sample of diaries and questionnaires using a secure double data entry system. Agreement of 99% was achieved. We

Table 1 Description of participants. Values are numbers (percentages) unless stated otherwise

Characteristics	Supplement group	Placebo group
	n=456	n=454
Median (interquartile range) age (years)	72 (68.0-76.0)	71 (68.0-76.0)
Aged ≥85	19 (4)	16 (4)
Women	217 (48)	214 (47)
Mean (SD) body mass index (kg/m^2)	28.2 (4.2)	27.9 (4.1)
	n=456	n=453
Current smoker	57 (13)	63 (14)
Current No of different drugs taken:	n=455	n=453
0-2	205 (45)	234 (52)
3-6	198 (44)	164 (36)
>6	52 (11)	55 (12)
Past and present chronic conditions:	n=456	n=454
Hypertension	188 (41)	172 (38)
Heart disorders	137 (30)	130 (29)
Chest disorders	86 (19)	87 (19)
Diabetes	37 (8)	42 (9)
Cancer	46 (10)	46 (10)
Cerebrovascular disease	31 (7)	22 (5)
Chronic infection present at recruitment	42 (9)	38 (8)
Injection in past year to prevent influenza	432 (95)	423 (93)
Place of residence:		
Community	440 (97)	439 (97)
Nursing home	16 (3)	15 (3)
Housing tenure:		
Owner occupier	340 (75)	332 (73)
Public sector tenant*	88 (19)	92 (20)
Other	28 (6)	30 (7)
Nutrient at high risk of being deficient†:		
Iron	73 (16)	37 (8)
Folate	25 (6)	21 (5)
Vitamin C	58 (13)	59 (13)
Vitamin D	70 (15)	49 (11)
At risk for any of above	145 (32)	117 (26)

*For example, council house tenant.
†On basis of micronutrient risk scores.

checked hospital records for all routinely collected data for everyone reporting a hospital admission or who had this documented in their general practice records. We entered a random sample of 10% of participants into the hospital's patient administration system to check whether any admissions had been missed; none were found. We used prespecified standardised procedures for extracting data from general practice and hospital records.

Participants were asked at the end of the study whether they knew their allocated treatment. Over 90% did not know or were unable to guess.

Statistical analysis

Each comparison was by intention to treat, irrespective of compliance with pill taking. Statistical significance for all primary and secondary end points was based on two sided tests, with $2P \leq 0.05$. We applied stricter levels of significance ($2P \leq 0.01$) to subgroup analyses. For skewed continuous data, we calculated median and interquartile ranges. To account for skewness, we used negative binomial and poisson regression models to estimate the incidence rate ratio and 95% confidence intervals between groups, adjusting for the minimisation covariates, using STATA.[18] We accounted for an excess number of zeroes in an outcome by using a zero inflated negative binomial or poisson model when appropriate.[19] A linear regression model in SPSS was used to estimate the mean difference for health related quality of life measures between groups, after adjusting for baseline values and the minimisation covariates.[20]

Results

Overall, 910 of 10 090 people (9%) aged 65 or over were recruited (fig 1). Only 13% (n = 121) of participants were lost to follow-up or reported stopping taking tablets. At least one diary was provided by 99% (901) of participants, six diaries by 93% (846), and 12 diaries by 89% (808).

Baseline data

The groups were well balanced at entry to the trial—for example, median age 72 and 71 in intervention and placebo groups (table 1). In total, 4% of participants were aged 85 or older; 3% lived in

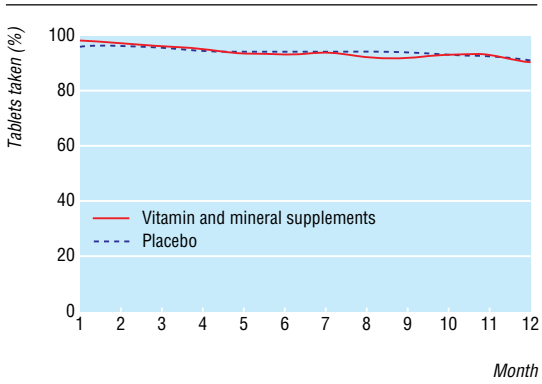

Fig 2 Compliance on basis of diaries completed by participants

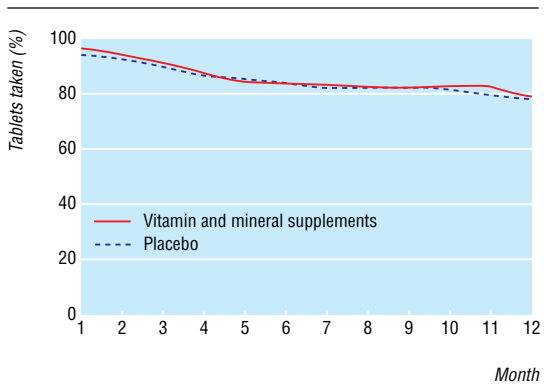

Fig 3 Compliance with zero intake imputed on non-return of diaries, including withdrawals. Participants who died were included up to point of censoring

nursing homes. Over half of the participants were men. More than half took three or more different drugs daily. Over 93% had had an injection in the previous year to prevent influenza.

On the basis of the questionnaire on nutrition, 32% of participants in the intervention group (n=145) and 26% in the placebo group (n=117) were at high risk of nutritional deficiency for iron, folate, vitamin C, or vitamin D. Slightly more people in the intervention group than in the placebo group were at high risk of iron deficiency (16% versus 8%).

Compliance

We found no differences between the groups for compliance with drug taking (figs 2 and 3). Compliance in participants still taking tablets and returning information in diaries was over 91% throughout the trial (fig 2). Compliance for all participants who had not died was over 78% throughout the trial (fig 3). Compliance as assessed by self report was consistent with tablet counting.

Outcomes

We found no statistically significant effect from supplementation on our primary outcomes of contacts with primary care staff (mostly general practitioners and practice nurses) and days of infection per person: incidence rate ratio 0.96, 95% confidence interval 0.78 to 1.19 and 1.07, 0.90 to 1.27; table 2). Supplementation did not seem to affect quality of life (table 3).

None of the secondary outcomes significantly differed between the groups (table 4).

Ancillary analyses and purported adverse events

Prespecified subgroup analyses for age, sex, and type of accommodation did not significantly differ between the groups (data not shown). Neither did we find important differences for subgroups on the basis of the nutrition risk score (no deficiency versus one deficiency in any of the four groups; table 5).

Purported adverse events were not serious (headache, insomnia, gout, for example). These events did not significantly differ between the groups (table 4). Similar numbers of participants in the groups died during the study (table 4).

Discussion

Regular use of commonly available multivitamin and multimineral supplements by community dwelling older people who do not already take supplements is unlikely to reduce the number of self reported infections or associated use of health services. It remains to be seen whether populations at higher risk of

Table 2 Contacts with primary care for infections and days of infection (including type) in community dwelling people aged 65 or older receiving multivitamin and multimineral supplementation or placebo for 12 months

	Supplement group		Placebo group		
Outcome measures	No	Median (interquartile range) per person	No	Median (interquartile range) per person	Incidence rate ratio (95% CI)
Contacts with primary care for infections*	879	1.0 (0-2)	930	1.0 (0-3)	0.96 (0.78 to 1.19); P=0.74
No in group	n=453	—	n=452	—	—
No of days of self reported infection†:	8072	7.0 (0-24)	7871	8.0 (0-23)	1.07 (0.90 to 1.27); P=0.41
Upper respiratory tract infections	4068	1.0 (0-10)	3826	1.0 (0-10.25)	—
Lower respiratory tract infections	1782	0	1436	0	—
Genitourinary tract infections	690	0	579	0	—
Skin infections	1106	0	1256	0	—
Other infections	426	0	774	0	—
No in group	n=451	—	n=450	—	—

*Negative binomial model.
†Zero inflated negative binomial model.

Table 3 Quality of life measures for community dwelling people aged 65 or older receiving multivitamin and multimineral supplementation or placebo for 12 months

	Supplement group		Placebo group			
Quality of life measures	No	Mean (SD)	No	Mean (SD)	Mean difference (95% CI)	P value
Euroqol						
Baseline	455	0.75 (0.2)	453	0.78 (0.2)	—	—
12 months	421	0.77 (0.2)	409	0.80 (0.2)	–0.019 (–0.040 to 0.002)	0.08
SF-12						
Baseline:						
Physical	454	42.8 (11.4)	452	43.8 (10.7)	—	—
Mental	454	53.4 (8.7)	452	54.0 (8.7)	—	—
12 months:						
Physical	415	43.7 (11.1)	412	44.3 (10.5)	0.07 (–0.90 to 1.03)	0.89
Mental	415	53.2 (9.1)	412	53.6 (9.2)	–0.03 (–1.11 to 1.05)	0.96

Table 4 Data on prescriptions for antibiotics, hospital admissions, and infections in community dwelling people aged 65 or older receiving multivitamin and multimineral supplementation or placebo for 12 months

	Supplement group		Placebo group			
Outcome measure	No	Median (interquartile) range per person	No	Median (interquartile range) per person	Incidence rate ratio (95% CI)	P value
No of prescriptions for antibiotics in primary care*	619 (n=453)	1.0 (0.0-2.0)	641 (n=452)	0.0 (0.0-2.0)	0.98 (0.80 to 1.20)	0.85
Days of antibiotic prescribed per person in primary care*	(n=197)	10.0 (7.0-20.5)	(n=191)	10.0 (7.0-21.0)	0.93 (0.78 to 1.12)	0.45
No of hospital admissions	150 (n=453)	0 (0)	125 (n=452)	0 (0)	1.22 (0.89 to 1.67)	0.21
No of admissions for treatment of infections†	22 (n=453)	0 (0)	23 (n=452)	0 (0)	0.97 (0.54 to 1.74)	0.92
Days of hospital stay for treatment of infections*	(n=15)	9.0 (4.0-16.0)	(n=16)	13.5 (6.25-34.5)	0.74 (0.40 to 1.37)	0.34
No of outpatient appointments for treatment of infections‡	34 (n=453)	0 (0)	41 (n=452)	0 (0)	0.80 (0.38 to 1.67)	0.56
No of outpatient appointments§	999 (n=440)	1.0 (0.0-3.0)	845 (n=435)	1.0 (0.0-3.0)	1.16 (0.92 to 1.47)	0.22
No of deaths¶	8 (n=456)		4 (n=454)		—	0.25
No of adverse events‡	28 (n=456)	0 (0)	37 (n=454)	0 (0)	0.64 (0.22 to 1.93)	0.43

*Negative binomial model.
†Poisson model.
‡Zero inflated poisson model.
§Zero inflated negative binomial model.
¶Pearson's χ^2=1.333.

Table 5 Subgroup analysis of contact with primary care for infection and days of infection by nutrition risk of community dwelling people aged 65 or older receiving multivitamin and multimineral supplementation for 12 months

	Supplement group		Placebo group		Incidence rate ratio at risk versus not at risk (99% CI)†	P value
Subgroup	Low risk	High risk	Low risk	High risk		
No of contacts with primary care staff for infections*:						
No at risk	309/453	144/453	336/452	116/452	—	—
Median (interquartile range) per person	1.0 (0.0-2.0)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	1.0 (0.0-4.0)	1.16 (0.64 to 2.12)	0.52
No of infection days per person‡:						
No at risk	307/451	144/451	334/450	116/450	—	—
Median (interquartile range) per person	7.0 (0.0-20.0)	7.5 (0.0-32.5)	7.0 (0.0-22.0)	13.0 (0.0-32.0)	1.04 (0.64 to 1.69)	0.84

High risk=at risk for one or more of following nutrient deficiencies: vitamin C, vitamin D, folate, or iron; low risk=not at risk for vitamin C, vitamin D, folate, or iron deficiency.
*Negative binomial model.
†Estimated from a treatment by nutrition risk interaction term.
‡Zero inflated negative binomial model.

infections, such as older people living in nursing homes, would benefit from supplementation.

Our population had few people aged 85 or older or in nursing homes, who may be at higher risk of nutritional deficiency.[5] Our population may have been healthier than people who did not volunteer for the study. We did not, however, recruit people already taking nutritional supplements (likely to be more than 25% of this age group[5]). By leaving out such people, we probably excluded those with healthier diets.[5] By using a simple questionnaire, we found that over 25% of the population was judged to be at high risk of nutritional deficiency and potentially more likely to benefit from supplementation, although this was not supported by our subgroup analyses. The proportion of the trial population at high risk of nutritional deficiency was similar to that in a community survey of older people in the same region of Scotland.[16]

Our participants were similar in age and place of residence to those studied in a previous, disputed trial that reported beneficial effects from supplementation.[7 9 10] Participants in that trial had levels of nutrient deficiencies (assessed by blood sampling) similar to people designated by our questionnaire as being at high risk of nutrient deficiency. Unlike our trial, the supplement used in the previous trial had four times the levels of vitamin E and vitamin B_{12} and also contained selenium, magnesium, calcium, and β carotene.[7]

Other randomised controlled trials have not found beneficial effects of multivitamin and multimineral supplements on risk of infection in community dwelling older people.[21–23] A trial in France reported no statistically significant effect of vitamin and mineral supplements on infections.[21] A study in the Netherlands found that multivitamin and multimineral supplements had no significant effect on acute respiratory tract infections.[22] A US study in primary care also found no significant effect from multivitamin and multimineral supplements on infections in people aged 65 and over.[23]

Supplementation, especially of trace elements, has been shown to reduce infections in older people in nursing care with higher levels of nutritional deficiency.[24] An effect of borderline significance was reported by another trial.[25] The effects of supplementation with vitamin E also seem to differ between community and nursing populations. In one study, vitamin E seemed to worsen the severity of infections in people living in the community,[22] whereas it reduced the number of respiratory tract infections in a trial of nursing home residents.[26]

We cannot exclude the possibility that the intakes provided in the supplement were inadequate to affect the immune system. Our trial was pragmatic, which examined participants' self reported infections and use of health services rather than confirming infection by rigorous criteria seldom used in

What is already known on this topic

The vitamin and mineral status of older people may be suboptimal, influencing immunity and risk of infection

It is unclear from previous trials in community dwelling older people whether multivitamin and multimineral supplements influence infection

What this study adds

Routine multivitamin and multimineral supplementation of older people living at home is unlikely to affect self reported infection related morbidity

Studies are needed in higher risk populations, such as older people living in nursing homes

practice. Errors in self reporting should be balanced between the two groups.

Other members of the MAVIS Trial Group were Kathryn Brownie (research assistant), Janice Cruden (trial secretary), Gladys McPherson (senior information technology manager), Clare Robertson (research assistant), and Joanne Warner (research assistant). Collaborators in primary care were: Ellon Health Centre—Alan Donaldson, Ian MacKay, Duncan McKerchar, Ian Simpson, Martin Pucci, Rosamund Bell, Peter Brown, Pilar Murphy, Huber Kam, Anne Pearson, and Caroline Cumming; Gilbert Road Medical Group—John Corse, Douglas Orr, Linda Sandilands, James Scott, Murdoch Shirreffs, Sheena Tuttle, Jane White, Gordon Wilson, Jane Harvey, and Hilary Andrew; Inverurie Health Centre—James Beattie, James Black, Victor Johnston, David Hood, Jacqueline MacDonald, Sally Harkness, Fiona McKay, David Rutledge, Fiona Baxter, Gillian Brewis, Richard Gordon, Eunice Connon, Wilma Hadden; Macduff Health Centre—Iain Brooker, Alison Barbour, Pat Hoddinott, Murial Barclay, and Joy Thom; Peterhead Health Centre—Lewis Ritchie, Kenneth Strachan, Patricia Donaldson, Joyce Robertson, John Stout, Ian Small, Gregor Bruce, David Kennedy, Bruce Strachan, Graham Strachan, Dale Fenwick, Michelle Bibby, Ethel Wilson, Fiona Begg; and Queen's Road Medical Group—Iain Duthie, Geoff Clarke, Fiona Garton, Eunice Connon, Paul Davidson, Iain Stirling, Theresa Suttle, Stuart Watson, Belinda Porter, Shona Nairn, Loraine Horsburgh, Rosie Jamieson. Group members of the Data Monitoring and Safety Committee were Adam Coldwells (chair), Barbara Golden, and Lewis Ritchie. We thank the participants and staff of the general practices and medical records at Aberdeen Royal Infirmary.

Contributors: AA, MKC, JAC, PCH, MMK, GMcN, ACM, CRR, DGS, AIS, and LDV (writing group of the MAVIS trial) designed the study, interpreted the data, wrote the paper, and approved the final version. AA is guarantor.

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1 *Morbidity statistics from general practice.* London: HMSO, 1995.
2 Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 2000;283:499-505.
3 Lesourd B. Immune response during disease and recovery in the elderly. *Proc Nutr Soc* 1999;58:85-98.
4 Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. *Am J Clin Nutr* 1997;66:S464-77.
5 *National diet and nutrition survey: people aged 65 years and over.* London: Stationery Office, 1998.
6 El-Kadiki A, Sutton AJ. Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2005;330:871-4.
7 Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. *Lancet* 1992;340:1124-7.
8 Chandra RK. Influence of multinutrient supplement on immune responses and infection-related illness in 50-65 year old individuals. *Nutr Res* 2002;22:5-11.
9 Meguid MM. Retraction. *Nutrition* 2005;21:286.
10 Sutton A, El-Kadiki A. Assessing concerns regarding the validity of three trials included in "Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials." http://bmj.bmjjournals.com/cgi/content/full/bmj.38399.495648.8F/DC2 (accessed 15 Jul 2005).
11 *Dietary reference values for food energy and nutrients for the United Kingdom. Report on health and social subjects No 41.* London, HMSO: 1991.
12 The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
13 Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. *How to score version 2 of the SF12 health survey (with a supplement documenting version 1).* Lincoln, RI: QualityMetric, 2002.
14 Kind P, Hardman G, Macran S. *UK population norms for EQ-5D.* Discussion paper 172. York; Centre for Health Economics, 1999.
15 *Nutrition assessment questionnaire.* http://www.foodfrequency.org/naq (accessed 15 Jun 2004).
16 McNeill G, Vyvyan J, Peace H, McKie L, Seymour G, Hendry J, et al. Predictors of micronutrient status in men and women over 75 years old living in the community. *Br J Nutr* 2002;88:555-61.
17 Medical Research Council. *MRC guidelines for good clinical practice in clinical trials.* London: MRC, 1998. http://www.mrc.ac.uk/pdf-ctg.pdf (accessed 15 Jun 2004).
18 *Stata statistical software: release 8.0.* College Station, TX: Stata; 2003.
19 Lambert D. Zero-inflated poisson regression, with an application to defects in manufacturing. *Technometrics* 1992;34:1-14.
20 *SPSS base 11.0 for Windows user's guide.* Chicago, IL: SPSS, 2001.
21 Chavance M, Herbeth B, Lemoine A, Zhu B-P. Does multivitamin supplementation prevent infections in healthy elderly subjects? A controlled trial. *Int J Vit Nutr Res* 1993;63:11-6.
22 Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory infections in elderly persons. A randomised controlled trial. *JAMA* 2002;288:715-21.
23 Barringer TA, Kirk JK, Santaniello AC, Foley KL, Michielutte R. Effect of a multivitamin and mineral supplement on infection and quality of life. A randomised, double-blind, placebo-controlled trial. *Ann Intern Med* 2003;138:365-71.
24 Girodon F, Lombard M, Galan P, Brunet-Lecomte P, Monget A-L, Arnaud J, et al. Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial. *Ann Nutr Metab* 1997;41:98-107.
25 Girodon F, Galan P, Monget A-L, Boutron-Ruault M-C, Brunter-Lecomte P, Preziosi P, et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients. A randomized controlled trial. *Arch Intern Med* 1999;159:748-54.
26 Meydani SM, Leka LS, Fine BC, Dallal GE, Keusch GT, Fiatarone Singh M, et al. Vitamin E and respiratory tract infections in elderly nursing home residents. A randomised controlled trial. *JAMA* 2004;292:828-36.

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